09/961,089

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Shahzi Iqbal, et al.

Assignee: Genexpress Informatics, Inc.

Title: PREFERENTIAL DISPLAY

Patent No.: 6,861,219 B2 Issued: March 1, 2005

Atty. Docket No.: 1495-0001

Certificate
MAR 23 2005
of Correction

MS: Certificate of Correction Branch
COMMISSIONER FOR PATENTS
PO Box 1450
Alexandria, VA 22313-1450

## REQUEST FOR CERTIFICATE OF CORRECTION OF PATENT— PTO MISTAKE (37 C.F.R. § 1.322(a))

Dear Sir:

Pursuant to 35 U.S.C. § 254 and 37 C.F.R. § 1.322(a), please issue a Certificate of Correction in the above-identified matter. The mistakes to be corrected were made by the Office.

1. Attached hereto, in duplicate, is Form PTO-1050, with at least one copy suitable for printing.

2. The exact pages and line numbers where the errors are shown correctly in the application file:

   Response to Office Action dated January 22, 2004: page 3, claim 5; page 4, claim 10; and page 5, claims 14, 16, and 17 (a copy of which, with corrections, is attached).

   Information Disclosure Statement by Applicant, signed by the Examiner, November 4, 2002, pages 1-2 (copy of which is attached).

3. Please send the Certificate to:

   Jeffrey G. Toler
   TOLER, LARSON & ABEL, LLP
   5000 PLAZA ON THE LAKE, SUITE 265
   AUSTIN, TX 78746

MAR 2 3 2005

Respectfully submitted,

3·18·05
Date

John R. Schell, Reg. No. 50,776
Agent for Applicants
TOLER, LARSON & ABEL, L.L.P.
P.O. Box 29567
Austin, Texas 78755-9567
(512) 327-5515 (phone)
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PTO/SB/44 (05-03)
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# UNITED STATES PATENT AND TRADEMARK OFFICE
## CERTIFICATE OF CORRECTION

PATENT NO : 6,861,219 B2

DATED : March 1, 2005

INVENTOR(S) : Iqbal, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 5, line 2, please change the word "stands" to --strands--.

In claim 10, line 1, please change "method of claim 1," to --method of claim 9--.

In claim 14, line 10, please change the word "stands" to –strands--.

In claim 16, line 2, please change the word "stands" to –strands--.

In claim 17, line 2, please change the word "stands" to –strands--.

MAILING ADDRESS OF SENDER:
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DATED : March 1, 2005

INVENTOR(S) : Iqbal, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the References Cited section, please add:

Lennon, G.G. (2000) High-throughput gene expression analysis for drug discovery. DDT, 5(2), 59-66

Artinger, M. et al. (1998) High throughput Analysis of Differential Gene Expression. J. Cell. Biochem. Suppl. 30/31, 286-296

Berk, A.J. & Sharp, P.A. (1977) Sizing and mapping of early adenovirus mRNAs by gel electrophoresis of S1 endonuclease-digested hybrids. Cell 12, 721-732

Lee, J.J. and Costlow, N.A. (1987) A molecular titration assay to measure transcript prevalence levels. Methods Enzymol. 152, 633-648

Hedrick, S.M. et al. (1984) Isolation of cDNA clones encoding T cell-specific membrane-associated proteins. Nature 308, 149-153

Swaroop, A. et al. (1991) A simple and efficient cDNA library subtraction procedure: Isolation of human retina-specific cDNA clones. Nucleic Acids Res. 25, 1954

Lisitsyn, N. et al. (1993) Cloning the differences between two complex genomes. Science 259, 946-951

Greenberg, M.E. and Ziff, E.B. (1984) Stimulation of 3T3 cells induces transcription of the c-fos proto-oncogene. Nature 311, 433-438

Marzluff, W.F. (1978) Transcription of RNA in isolated nuclei. Methods Cell Biol. 19, 317-331

Manley, J.L. and Gefter, M.L. (1981) Transcription of mammalian genes in vitro. Gene Amplif. Anal. 2, 369-382

Liang, P. and Pardee, A.B. (1992) Differential display of eukaryotic messenger RNA by means of the polymerase chain reaction, Science 257, 967-997

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DATED : March 1, 2005

INVENTOR(S) : Iqbal, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the References Cited section, please add:

Zhang, L. et al. (1997) Gene expression profiles in normal and cancer cells. Science 276, 1268-1272

Polyak, K. et al. (1997) A model for p53-induced apoptosis. Nature 389, 300-305

Schena M. et al. (1995) Quantitative monitoring of gene expression patterns with a complementary DNA microarray. Science 270, 467-470

Lennon, G.G. et al. (1996) the I.M.A.G.E. consortium: An integrated molecular analysis of genomes and their expression. Genomics 33, 151-152

Heller, R.A. et al. (1997) Discovery and analysis of inflammatory disease-related genes using cDNA microarrays. Proc. Natl. Acad. Sci. U.S.A. 94, 2150-2155

Schena, M. et al. (1996) Parallel human genome analysis: Microarray-based expression monitoring of 1000 genes. Proc. Natl. Acad. Sci. U.S.A. 93, 10614-10619

Gress, T. et al. (1992) Genome 3:609-619.

Southern, E.M. (1975) J. Mol. Biol. 98: 503-517.

Gray, N.S. et al. (1998) Exploiting chemical libraries, structure, and genomics in the search for kinase inhibitors. Science 281, 533-538

Marton, M.J. et al. (1998) Drug target validation and identification of secondary drug target effects using DNA microarrays. Nat. Med. 4, 1293-1301

Braxton, S. and Bedilion, T. (1998) The integration of microarray information in the drug development process. Curr. Opin. Biotechnol. 9, 643-649

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PATENT

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| | | | |
|---|---|---|---|
| Applicant(s): | Shahzi Iqbal et al. | | |
| Title: | PREFERENTIAL DISPLAY | | |
| App. No.: | 09/961,089 | Filed: | 09/24/2001 |
| Examiner: | Alexander H. Spiegler | Group Art Unit: | 1637 |
| Atty. Dkt. No.: | 1495-0001 | | |

MS NON-FINAL AMENDMENT
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

## RESPONSE TO OFFICE ACTION

Dear Sir:

In response to the Office Action mailed January 16, 2004, please amend the above-identified application as follows:

CERTIFICATE OF TRANSMISSION/MAILING
I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to the Commissioner for Patents on 1-22-04.

Elise K. Daugherty
Typed or Printed Name

E K Daugherty
Signature

MAR 2 3 2005

## SPECIFICATION AMENDMENTS:

Please amend the Specification as indicated:

Please amend paragraph [0017] as follows:

[0017] FIG. 1 is a schematic diagram illustrating the preferential display technique. The figure shows the end products of unique RNA and cDNA strands isolated after degradation of the cDNA/RNA ~~compliments~~ complements. FIG 2 is a schematic diagram of the final treatment with RNase to degrade the single stranded RNA's present in each sample and the PCR amplification of the isolated cDNA which are uniquely expressed in each sample.

Please amend paragraph [0019] as follows:

[0019] The invention is a method called Preferential Display. The approach starts with the sample collection and categorizing of the cells, tissues or blood samples. Once the normalized control cells are isolated from the diseased state, expressed RNA's are isolated using standard methods. The RNA's are then placed into two tubes of normal and the other diseased RNA's for a total of four tubes. One normal and diseased are then RT-PCR with dye labeled oligos producing fluorescence labelled cDNA's in each tube. At this point of the reaction, RNA's of normal and diseased are added to their complementary tubes, normalized cDNAs with diseased RNAs and diseased cDNAs with normalized RNAs. Common sequences in each tube hybridize to form cDNA/RNA ~~compliments~~ complements. The tubes are then treated with Exonuclease III or VII to degrade all the hybridized complements. RNase is then added to digest the single stranded RNA's in each tube. The remaining undigested cDNA are unique dye labeled sequences expressed in either normal or diseased states. Additional PCR can be ran to increase the cDNA present in each tube before running on a gel or high throughput sequencer.

## CLAIM AMENDMENTS:

Please amend the claims as indicated:

1-26. *(CANCELED)*

(1) 26. *(CURRENTLY AMENDED)* A method for eliminating redundant sequences that are common between two samples, the method comprising of the steps:

isolating RNA strands from a first sample;

isolating RNA strands from a second sample;

generating cDNA strands from the RNA strands from the first sample;

mixing the cDNA strands of the first sample with the RNA strands from the second sample;

hybridizing the cDNA strands and RNA strands with common sequences to form cDNA/RNA ~~compliments~~ complements, the cDNA strands and the RNA strands without common sequences remaining unhybridized cDNA strands and unhybridized RNA strands; and

degrading the cDNA/RNA ~~compliments~~ complements to leave the unhybridized cDNA strands and the unhybridized RNA strands.

(2) 27. *(PREVIOUSLY PRESENTED)* The method of Claim (1) 26, wherein the step of generating cDNA strands from the RNA strands from the first sample comprises performing RT-PCR.

28. *(CANCELLED)*

(3) 29. *(PREVIOUSLY PRESENTED)* The method of Claim (1) 26, wherein the first sample is a healthy tissue and the second sample is a diseased tissue.

(4) 30. *(PREVIOUSLY PRESENTED)* The method of Claim (1) 26, wherein the first sample is a diseased tissue and the second sample is a healthy tissue.

(5) 31. *(PREVIOUSLY PRESENTED)* The method of Claim (1) 26, further comprising:

amplifying the unhybridized cDNA strands using PCR.

(6) 32. *(PREVIOUSLY PRESENTED)* The method of Claim ~~26~~ (1), further comprising:
producing a second set of cDNA strands from the unhybridized RNA strands.

(7) 33. *(PREVIOUSLY PRESENTED)* The method of Claim ~~32~~ (6), further comprising:
amplifying the second set of cDNA strands using PCR.

(8) 34. *(CURRENTLY AMENDED)* The method of Claim ~~26~~ (1), wherein the step of degrading ~~compliments~~ complements is performed with an Exonuclease III enzyme.

35. *(CANCELLED)*

(9) 36. *(PREVIOUSLY PRESENTED)* The method of Claim ~~26~~ (1), further comprising:
displaying at least one of the unhybridized cDNA strands and the unhybridized RNA strands.

(10) 37. *(PREVIOUSLY PRESENTED)* The method of Claim ~~36~~ (9), wherein the step of displaying comprises using electrophoresis.

(11) 38. *(PREVIOUSLY PRESENTED)* The method of Claim ~~26~~ (1), further comprising:
reading at least one of the unhybridized cDNA strands and the unhybrized RNA strands with an autoradiogram.

(12) 39. *(PREVIOUSLY PRESENTED)* The method of Claim ~~26~~ (1), wherein the first and second samples are selected from the group consisting of cells, tissues, pathogens, plants, and animals.

(13) 40. *(PREVIOUSLY PRESENTED)* The method of Claim ~~26~~ (1), wherein the first and second sample are differentiated due to a diseased state, developmental change, or induced by an external or internal stimulus.

(14) 41. *(CURRENTLY AMENDED)* A method for determining differences between a first sample of cDNA strands and a second sample of RNA strands, the method comprising of the steps:

mixing the first sample of cDNA strands with the second sample of RNA strands;

hybridizing the cDNA strands and the RNA strands with common sequences to form cDNA/RNA ~~compliments~~ complements, the cDNA strands and the RNA strands without common sequences ~~remaning~~ remaining unhybridized cDNA strands and unhybridized RNA strands;

degrading the cDNA/RNA ~~compliments~~ complements to leave the unhybridized cDNA strands and the unhybridized RNA strands; and

analyzing at least one of the unhydridized cDNA strands and the unhybridized RNA strands to determine differences between the first sample and the second sample.

42. *(CANCELLED)*

(15) 43. *(PREVIOUSLY PRESENTED)* The method of Claim (14) 41, further comprising:

amplifying the unhybridized cDNA strands using PCR.

(16) 44. *(PREVIOUSLY PRESENTED)* The method of Claim (14) 41, further comprising:

producing a further set of cDNA strands from the unhybridized RNA strands.

(17) 45. *(PREVIOUSLY PRESENTED)* The method of Claim (16) 44, further comprising:

amplifying the further set of cDNA strands using PCR.

(18) 46. *(CURRENTLY AMENDED)* The method of Claim (14) 41, wherein the step of degrading ~~compliments~~ complements is performed with an Exonuclease III enzyme.

47. *(CANCELLED)*

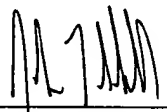
## REMARKS

With respect to items 1 and 2 of the Office Action mailed January 16, 2004, Applicants appreciate Examiner Spiegler's consideration of the Amendment. With respect to item 3, Applicants have amended claims 26, 34, 41, and 46 and have submitted amended paragraphs 0017 and 0019. The claim amendments were made to correct typographical errors and were not made to overcome prior art for reasons of novelty or obviousness. With respect to item 4, Applicants have cancelled claim 35 and 47. Applicants respectfully traverse the rejection, but have canceled the claims in order to expedite issuance.

Applicants agree with Examiner Spiegler's assessment and respectfully submit that the present application is now in condition for allowance. Accordingly, the Examiner is requested to issue a Notice of Allowance for all pending claims.

Should the Examiner deem that any further action by Applicants would be necessary for placing this application in condition for issue, the Examiner is requested to contact the undersigned agent by telephone at the number listed below.

Respectfully submitted,



1.22.04
Date

John R. Schell, Reg. No. 50,776
Attorney for Applicant(s)
TOLER, LARSON & ABEL, L.L.P.
P.O. Box 29567
Austin, Texas 78755-9567
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(use as many sheets as necessary)*

Sheet 1 of 2

| Complete If Known | |
|---|---|
| Application Number | |
| Filing Date | |
| First Named Inventor | SHAHZI LABAL |
| Group Art Unit | |
| Examiner Name | |
| Attorney Docket Number | |

JC679 U.S. PTO 09/961089 09/24/01

| OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS | | | |
|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
| AS | 1. | Lennon, G.G. (2000) High-throughput gene expression analysis for drug discovery. DDT, 5(2), 59-66 | |
| | 2. | Artinger, M. et al. (1998) High throughput Analysis of Differential Gene Expression. J. Cell. Biochem. Suppl. 30/31, 286-296 | |
| | 3. | Berk, A.J. & Sharp, P.A. (1977) Sizing and mapping of early adenovirus mRNAs by gel electrophoresis of S1 endonuclease-digested hybrids. Cell 12, 721–732 | |
| | 4. | Lee, J.J. and Costlow, N.A. (1987) A molecular titration assay to measure transcript prevalence levels. Methods Enzymol. 152, 633–648 | |
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| | 6. | Swaroop, A. et al. (1991) A simple and efficient cDNA library subtraction procedure: Isolation of human retina-specific cDNA clones. Nucleic Acids Res. 25, 1954 | |
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| AS | 11. | Liang, P. and Pardee, A.B. (1992) Differential display of eukaryotic messenger RNA by means of the polymerase chain reaction. Science 257, 967–997 | |

| Examiner Signature | Alexander H. Spiegel | Date Considered | 11/4/02 |
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(use as many sheets as necessary)*

Sheet 2 of 2

| Complete if Known | |
|---|---|
| Application Number | |
| Filing Date | |
| First Named Inventor | SHAHZI IQBal |
| Group Art Unit | |
| Examiner Name | |
| Attorney Docket Number | |

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09/24/01

| OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS | | | |
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| AD | 12. | Zhang, L. et al. (1997) Gene expression profiles in normal and cancer cells. Science 276, 1268–1272 | |
| | 13. | Polyak, K. et al. (1997) A model for p53-induced apoptosis. Nature 389, 300–305 | |
| | 14. | Schena, M. et al. (1995) Quantitative monitoring of gene expression patterns with a complementary DNA microarray. Science 270, 467–470 | |
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| | 16. | Heller, R.A. et al. (1997) Discovery and analysis of inflammatory disease-related genes using cDNA microarrays. Proc. Natl. Acad. Sci. U. S. A. 94, 2150–2155 | |
| | 17. | Schena, M. et al. (1996) Parallel human genome analysis:Microarray-based expression monitoring of 1000 genes. Proc.Natl.Acad.Sci. U.S.A. 93, 10614–10619 | |
| | 18. | Gress, T. et.al. (1992) Genome 3:609-619. | |
| | 19. | Southern, E.M. (1975) J. Mol. Biol. 98:503-517. | |
| | 20. | Gray, N.S. et al. (1998) Exploiting chemical libraries, structure, and genomics in the search for kinase inhibitors. Science 281, 533–538 | |
| | 21. | Marton, M.J. et al. (1998) Drug target validation and identification of secondary drug target effects using DNA microarrays. Nat. Med. 4, 1293–1301 | |
| AD | 22. | Braxton, S. and Bedilion, T. (1998) The integration of microarray information in the drug development process. Curr. Opin. Biotechnol. 9, 643–649 | |

| Examiner Signature | Alexander H. Spiegel | Date Considered | 11/4/02 |
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